VI. Drug Therapy

1. Thresholds and goals for drug treatment

a. Drug therapy to achieve treatment goals: overview

LDL cholesterol is the primary target of treatment in clinical lipid management. The use of therapeutic lifestyle changes (TLC), including LDL-lowering dietary options (plant stanols/sterols and increased viscous fiber) will achieve the therapeutic goal in many persons. Nonetheless, a portion of the population whose short-term and/or long-term risk for CHD, will require LDL-lowering drugs to reach the prescribed goal for LDL cholesterol. The availability of HMG CoA reductase inhibitors (statins) allows attainment of the LDL goal in most higher risk persons. Other agents—bile acid sequestrants, nicotinic acid, and some fibrates—also can moderately lower LDL levels.

If TLC alone fails to achieve the goal for LDL cholesterol, consideration can be given to adding drug therapy. In such cases, the third visit of dietary therapy (Figure V.2–1) will be the visit to initiate drug treatment. When drugs are used, however, TLC also should always be used concomitantly. Dietary therapy provides additional CHD risk reduction beyond drug efficacy. Suggestions for combined use of TLC and drug therapy are given in Table VI.1–1.

The general scheme for initiation and progression of LDL-lowering drug therapy is outlined in Figure VI.l–l. As with dietary therapy, the first priority of drug therapy is to achieve the goal for LDL cholesterol. For this reason an LDL-lowering drug should be started. The usual drug will be a statin, but alternatives are a bile acid sequestrant or nicotinic acid. The starting dose of statin will depend on the baseline LDL-cholesterol level. In persons with only moderate elevations of LDL cholesterol, the LDL-cholesterol goal will be achieved with low or standard doses, and higher doses will not be necessary. The response to drug therapy should be checked in about 6 weeks. If the treatment goal has been achieved, the current dose can be maintained; if not, LDL-lowering therapy can be intensified, either by increasing the statin dose or by combining a statin with a bile acid sequestrant.

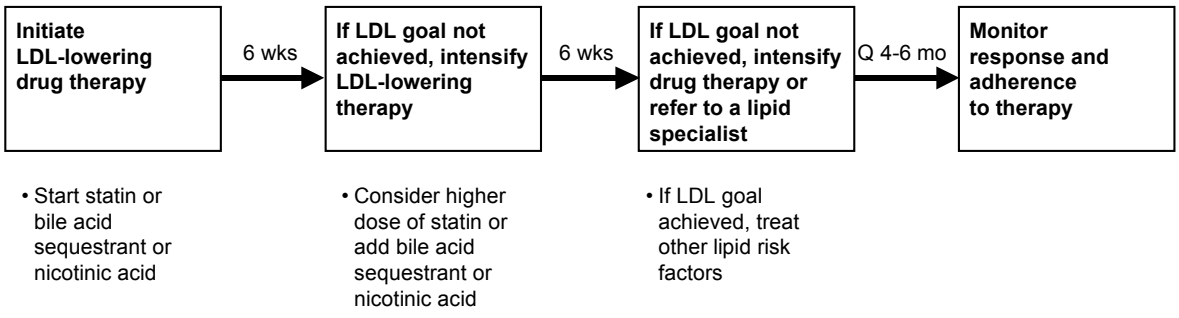
Although LDL cholesterol is the primary target of therapy, other lipid risk factors besides elevated LDL affect CHD risk. Among these are low HDL cholesterol, elevated triglyceride (especially VLDL remnants), and possibly small LDL particles. This "lipid triad" has been called *atherogenic dyslipidemia.* It commonly occurs as one component of the metabolic syndrome. Weight reduction and increased physical activity constitute first-line therapy for atherogenic dyslipidemia, and three classes of drugs—statins, nicotinic acid, and fibrates—favorably modify the lipid abnormalities of atherogenic dyslipidemia. Many persons with atherogenic dyslipidemia have high triglycerides ($\geq$200 mg/dL). Such persons usually have an increase in atherogenic VLDL remnants, which can be estimated clinically by measuring VLDL cholesterol. In persons with high triglycerides, the combination of LDL cholesterol + VLDL cholesterol (non-HDL cholesterol) represents *atherogenic cholesterol*. Non-HDL cholesterol thus represents a secondary target of therapy (after LDL cholesterol) when triglycerides are elevated. Statins alone will be sufficient to attain the non-HDL-cholesterol goal in some persons, but a combination of statins and nicotinic acid (or fibrates) can be helpful in others.

Table VI.1–1. Suggestions for Combined Use of TLC and Drug Therapy

• Intensive LDL lowering with TLC, including therapeutic dietary options (plant stanols/sterols and/or increased viscous fiber) – May obviate need for drug therapy – Can augment LDL-lowering drug therapy – May allow for lower doses of drugs
• Weight control plus increased physical activity – Reduces risk beyond LDL-cholesterol lowering – Constitutes primary management of the metabolic syndrome – Raises HDL-cholesterol levels – Enhances reduction of non-HDL cholesterol
• Initiating TLC before drug consideration – For most persons, a trial of dietary therapy of about 3 months is advised before initiating drug therapy – Unsuccessful trials of dietary therapy without drugs should not be prolonged indefinitely if goals of therapy are not approached in a reasonable period; drug therapy should not be withheld if it is needed to reach targets in persons with a short-term and/or long-term CHD risk that is high.
• Initiating drug therapy simultaneously with TLC – For severe hypercholesterolemia in which dietary therapy alone cannot achieve LDL targets – For those with CHD or CHD risk equivalents in whom dietary therapy alone will not achieve LDL targets

The general strategy for initiation and progression of drug therapy is outlined in Figure VI.1–1. Consideration of drug therapy often occurs simultaneously with the decision to initiate TLC therapy for the metabolic syndrome (Figure V.2–1). Thus weight reduction and increased physical activity may begin at the same time as drug treatment.

Figure VI.1–1. Progression of Drug Therapy



After another 6 weeks, the response to therapy should be assessed. If the LDL-cholesterol goal is still not achieved, further intensification of therapy should be considered, with re-evaluation in another 6 weeks. Once the LDL-cholesterol goal has been attained, attention turns to other lipid risk factors when present. If triglycerides are high ($\geq$200 mg/dL), the secondary target of

treatment becomes non-HDL cholesterol. If the LDL-cholesterol goal has been attained but not the non-HDL-cholesterol goal, there are two alternative approaches: (a) the dose of the LDL-lowering drug can be increased to reduce both LDL and VLDL, or (b) consideration can be given to adding a triglyceride-lowering drug (fibrate or nicotinic acid) to LDL-lowering therapy, which will mainly lower VLDL (see Section VII). The latter approach has the advantage of raising HDL cholesterol in addition to lowering non-HDL cholesterol. Thereafter, persons can be monitored for response to therapy every 4 or 6 months, or more often if considered necessary.

Some cholesterol-lowering agents are currently available over-the-counter (OTC) (e.g., nicotinic acid), and manufacturers of several classes of LDL-lowering drugs (e.g., statins, bile acid sequestrants) have applied to the Food and Drug Administration (FDA) to allow these agents to become OTC medications. At the time of publication of ATP III, the FDA has not granted permission for OTC status for statins or bile acid sequestrants. If an OTC cholesterol-lowering drug is or becomes available, patients should continue to consult with their physicians about whether to initiate drug treatment, about setting goals of therapy, and about monitoring for therapeutic responses and side effects.

b. Cholesterol management in persons with CHD or CHD risk equivalents

The general approach to drug therapy in persons with CHD or CHD risk equivalents is shown in Figure IV.2–1. The LDL-cholesterol goal is <100 mg/dL. Most persons with CHD or CHD risk equivalents should be treated to achieve this goal. Special considerations for LDL-lowering therapy with drugs are given for the following subcategories of persons with CHD or CHD risk equivalents.

1) Baseline LDL cholesterol ≥130 mg/dL

Secondary prevention trials consistently show benefit from LDL-lowering drugs when baseline LDL cholesterol is ≥130 mg/dL. Thus, most persons with baseline LDL cholesterol ≥130 mg/dL should be started on LDL-lowering drugs simultaneously with TLC since many such persons cannot achieve the LDL-cholesterol goal of <100 mg/dL on dietary therapy alone. Nonetheless, the use of dietary therapy is essential because it provides benefits not available through drugs. In some persons, to achieve the LDL goal, relatively high doses of LDL-lowering drugs will be required. Statins typically are the drug of first choice. In persons whose baseline LDL cholesterol is very high, drugs in combination (e.g., statins + bile acid sequestrants) will be necessary to reduce the LDL cholesterol to <100 mg/dL.

2) On-treatment LDL cholesterol 100–129 mg/dL

If the LDL-cholesterol level is reduced to <100 mg/dL, current drug therapy can be continued. However, even in controlled clinical trials, less than half of persons with CHD achieved an LDL-cholesterol goal of <100 mg/dL on standard doses of statins (i.e., simvastatin 20–40 mg/day in the 4S trial or pravastatin 40 mg/day in CARE and LIPID). In the majority of participants, on-treatment LDL cholesterol was in the range of 100–129 mg/dL. For such persons, several therapeutic options are available (Table VI.1–2).

Table VI.1–2. Therapeutic Options for Clinical Management of Persons with On-Treatment LDL-Cholesterol Levels of 100–129 mg/dL

#1	• Increase intensity of TLC for LDL lowering to achieve LDL-cholesterol goal <100 mg/dL – Reinforce reduction of saturated fats and cholesterol – Add other dietary therapies ▸ Plant stanols/sterols ▸ Increase viscous fiber – Promote weight loss in overweight/obese persons
#2	• Intensify LDL-lowering drug therapy to achieve LDL-cholesterol goal <100 mg/dL – Increase dose of statin – Add a second LDL-lowering drug (bile acid sequestrant or nicotinic acid)
#3	• Introduce lifestyle therapies for treatment of the metabolic syndrome, if present – Promote weight loss in overweight/obese persons – Recommend increased physical activity
#4	• Employ drug therapy for treatment of atherogenic dyslipidemia, if present – Nicotinic acid – Fibric acids
#5	• Intensify treatment of nonlipid risk factors – Hypertension – Hyperglycemia – Prothrombotic state (antiplatelet drugs/anticoagulants)

First, dietary options for LDL lowering can be intensified. These include reinforcement of lifestyle therapies (reduced intakes of saturated fat and cholesterol and weight reduction); referral to a dietitian for medical nutrition therapy is advisable. These changes in eating habits, combined with other dietary therapies (plant stanols/sterols and increased viscous fiber), often will reduce LDL-cholesterol levels to near 100 mg/dL. *Second,* LDL-lowering drug therapy can be intensified. The dose of statins can be increased, or a second LDL-lowering drug (bile acid sequestrant or nicotinic acid) can be combined with statin therapy. *Third,* if the patient has the metabolic syndrome, attention can turn to managing this condition through weight loss and increased physical activity; besides improvement of lipid and nonlipid risk factors of this syndrome, further LDL lowering often is obtained. *Fourth,* if the patient has atherogenic dyslipidemia, other drugs (nicotinic acid or fibric acids) can be added to the regimen, or LDL-lowering therapy can be intensified. Nicotinic acid not only will improve atherogenic dyslipidemia, but it also can lower LDL-cholesterol levels. If elevated triglycerides are present, addition of one of these drugs will assist in reaching the non-HDL-cholesterol goal. And *fifth,* treatment of nonlipid risk factors can be intensified. Finally, a combination of these options is advisable for some persons.

3) Baseline LDL cholesterol 100–129 mg/dL

NHANES III data showed that more than 30 percent of people with CHD have baseline LDL-cholesterol levels in the 100–129 mg/dL range. In clinical practice, however, misclassification of LDL-cholesterol levels from single measurements in individuals will be high. Many persons will have true baseline LDL-cholesterol levels $\geq$130 mg/dL. Baseline levels of LDL cholesterol are labile from one measurement to another. Regardless of apparent baseline level, the LDL-

cholesterol goal for all CHD patients is <100 mg/dL. The various options outlined in Table VI.1–2 can be applied to this category. Many persons with baseline LDL-cholesterol levels between 100 and 129 mg/dL will be able to attain LDL cholesterol <100 mg/dL through TLC especially if it includes plant stanols/sterols and increased viscous fiber. Others will require cholesterol-lowering drugs to reach this target. Clinical judgment is required as to when to initiate a cholesterol-lowering drug. If the LDL cholesterol falls near 100 mg/dL on dietary therapy alone, the physician has the option to forego a cholesterol-lowering drug for the present. This is particularly so if other lipid or nonlipid risk factors seem to need greater attention.

Once adequate LDL-lowering therapy has been attained, other lipid risk factors deserve attention. For example, if the patient has an elevated triglyceride or low-HDL cholesterol, a different lipid-lowering drug can be considered (e.g., nicotinic acid or fibric acid). The positive results of the VA-HIT trial showing the efficacy of gemfibrozil therapy alone in CHD patients have led some authorities to favor fibrates over statins in low-LDL patients with CHD. Overall, however, for monotherapy, clinical trials with statins have been more robust in their favorable outcomes than have fibrates. In addition, combined drug therapy (low-dose statin + fibrate [or nicotinic acid]) remains an option in such persons, provided that precautions are taken to prevent and monitor for side effects of lipid-lowering drugs used in combination.

4) Baseline LDL cholesterol <100 mg/dL

Some patients with CHD or CHD risk equivalent will have a baseline LDL cholesterol <100 mg/dL. These patients are already at their LDL-cholesterol goal. For them, further LDL lowering is not required. Attention shifts to other lipid or nonlipid risk factors. If triglycerides are elevated ($\geq$200 mg/dL), the non-HDL cholesterol remains a secondary target of therapy. Alternative therapies to reduce VLDL-cholesterol levels to attain the non-HDL-cholesterol goal are statins or triglyceride-lowering drugs (nicotinic acid or fibrate). Furthermore, nonlipid risk factors may be largely responsible for the patient's CHD and thus may deserve intensive modification.

5) Initiating cholesterol-lowering drugs in hospitalized patients

Hospitalization for a coronary event or procedure provides a unique opportunity to initiate LDL-lowering therapy. Physicians should take advantage of this opportunity. In the past, this opportunity has often been lost due to confusion about the meaning of LDL-cholesterol levels obtained during hospitalization. Although it is true that LDL levels can change during an acute illness, this should not stand in the way of starting needed therapy. A few simple recommendations can guide initiation of LDL-lowering therapy during hospitalization. The guiding principle is that LDL cholesterol should be measured in all patients, preferably on admission, but in any case at some time during hospitalization, and can be used as a guide to start treatment (Ryder et al., 1984). Thus, the first 24 hours of hospital admission should be considered a "window of opportunity" during which a fasting lipoprotein profile should be obtained. Whereas as much as a 10 percent fall in LDL cholesterol may occur during this first day (due to heparinization, stress, diet, and other factors), a value quite close to the actual baseline for that individual will be obtained and will be crucial in the decision to initiate early cholesterol-lowering therapy.

If this first 24-hour "window" is missed, a fasting lipoprotein profile should still be obtained during hospitalization since an elevated LDL cholesterol in that setting will identify persons with even higher baseline LDL cholesterol. The following summarizes the ATP III position on initiation of LDL-lowering drugs during hospitalization of CHD-related events or procedures.

First, persons hospitalized with a coronary event or procedure should be discharged on *both* dietary therapy and drug therapy if the LDL cholesterol is ≥130 mg/dL.

Second, if the LDL is 100–129 mg/dL during hospitalization, clinical judgment should be used in deciding whether to initiate drug treatment at discharge. The initial LDL-cholesterol level obtained in the hospital may be the lowest value seen for this patient. LDL-cholesterol levels are decreased beginning in the first 24–48 hours after an event and may remain low for many weeks. Later, if necessary, therapy can be adjusted according to the LDL response.

Initiation of both TLC and LDL-lowering drugs at the time of hospital discharge has several advantages. First, at this time persons are particularly motivated to undertake and adhere to risk-lowering interventions. Second, failure to initiate indicated therapy early is one of the causes of a large "treatment gap" as outpatient follow up is often less consistent and more fragmented. Finally, new and ongoing studies suggest a very early benefit of LDL-cholesterol-lowering therapy (Arntz et al., 2000; O'Driscoll et al., 1997; Stenestrand and Wallentin, 2001; Stroes et al., 1995; Tamai et al., 1997). Recent support for this approach comes from the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Trial of over 3,000 persons hospitalized with non-Q myocardial infarction or unstable angina, with a mean hospital LDL-cholesterol level of 124 mg/dL. Statin treatment, initiated in the hospital, was safe and resulted in a 16 percent relative risk reduction in subsequent coronary events at 16 weeks (Schwartz et al., 2001). Finally, a large observational study from Sweden showed an adjusted 25 percent reduction in total mortality at one year for myocardial infarction patients started on statins in-hospital (Stenestrand 2001).

These latter trials (Schwartz et al., 2001 and Strenestrand 2001), while suggesting benefit from starting LDL-lowering therapy at time of acute coronary syndrome, do not preclude the need for further research on efficacy of drug therapy started at this time.

6) Special considerations for drug therapy in CHD patients

In most persons with CHD, goals for LDL-lowering therapy can be achieved with lifestyle therapies and drug monotherapy. The benefits of intensive LDL reduction with the use of drugs apparently extend to those with advanced age and poor cardiac prognosis; nonetheless, some persons with severe co-existing medical conditions that severely impair quality of life or life expectancy will not benefit.

A low HDL cholesterol (<40 mg/dL) is common in patients with CHD. A low HDL level can be secondary to other modifiable risk factors such as cigarette smoking, obesity, or physical inactivity. Beta-blockers can also lower HDL-cholesterol levels in CHD patients, but have been shown to be efficacious for reducing subsequent CHD events after myocardial infarction. Therefore, their benefit in CHD patients outweighs the drawback of HDL lowering. Secondary prevention trials show that statin therapy significantly reduces risk for major coronary events

even in patients with low HDL cholesterol; therefore in these patients, LDL remains the primary target of therapy. The VA-HIT study (Rubins et al., 1999) suggests that fibrate therapy also may be beneficial for patients with low HDL levels in whom LDL-cholesterol levels are near optimal.

c. General principles of primary prevention with drug therapy

Primary prevention pertains to individuals without clinically evident CHD. For those with CHD risk equivalents, primary and secondary prevention merge. The guidelines for consideration of drug therapy and target goals for primary prevention are shown in Table VI.1–3.

Table VI.1–3. Drug Therapy Consideration and Goals of Therapy for Primary Prevention

Risk Category	10-Year Risk for CHD	LDL cholesterol	
		Level at Which to Consider Drug Therapy	Primary Goal of Therapy
Multiple (2+) risk factors	>20% (includes all CHD Risk Equivalents*)	>100 mg/dL†	<100 mg/dL
	10–20%	≥130 mg/dL‡	<130 mg/dL
	<10%	≥160 mg/dL	<130 mg/dL
0–1 risk factor	<10%	≥190 mg/dL¥	<160 mg/dL

* Most patients with CHD risk equivalents have multiple risk factors and a 10-year risk >20 percent. They include patients with non-coronary forms of clinical atherosclerosis, diabetes, and multiple (2+) risk factors with a 10-year risk >20 percent by Framingham scoring.

† When LDL cholesterol is ≥130 mg/dL, a cholesterol-lowering drug can be started concomitantly with TLC. If baseline LDL cholesterol is 100–129 mg/dL, TLC should be started immediately. Concomitant use of drugs is optional; several options for drug therapy are available (e.g., statins, bile acid sequestrants, fibrates, nicotinic acid).

‡ When LDL cholesterol is in the range of 130–159 mg/dL, drug therapy can be used if necessary to reach the LDL-cholesterol goal of <130 mg/dL, after an adequate trial of TLC.

¥ When LDL cholesterol is in the range of 160–189 mg/dL, use of cholesterol-lowering drugs is optional, depending on response to TLC diet.

d. Drug considerations for persons with multiple (2+) risk factors

1) 10-year risk >20 percent

Persons with multiple (2+) risk factors whose 10-year risk for hard CHD is >20 percent are included in the category of CHD risk equivalent. As discussed in section VI.1.b, they are managed similarly to other CHD risk equivalents that include non-coronary forms of clinical atherosclerotic disease and diabetes. The LDL cholesterol goal in these patients is <100 mg/dL, and when LDL cholesterol is ≥130 mg/dL, an LDL-lowering drug can be started together with theraputic lifestyle changes. When baseline LDL cholesterol is 100–129 mg/dL, TLC is indicated and concomitant use of drugs is optional. Drug options include statins, bile acid sequestrants, fibrates, and nicotinic acid.

2) 10-year risk 10–20 percent

Here the LDL-cholesterol goal is <130 mg/dL. TLC should be introduced first. If this goal is not achieved after 3 months of TLC, drug therapy should be considered. A low dose of drug may suffice if TLC drops the LDL cholesterol to near 130 mg/dL. If not, a higher dose can be used. At the same time, if the metabolic syndrome is present, weight reduction and physical activity should be emphasized. Later, consideration can be given to modifying other lipid risk factors with nicotinic acid or fibrates if they have not been adequately controlled by TLC.

3) 10-year risk <10 percent

The LDL-cholesterol goal for multiple risk factors and 10-year risk <10 percent also is <130 mg/dL. However, LDL-lowering drugs are not to be considered unless LDL cholesterol remains ≥160 mg/dL on TLC. When 10-year risk is <10 percent, cost-effectiveness of drug therapy begins to erode, especially when the LDL-cholesterol level remains in the range of 130 to 159 mg/dL and other risk factors are appropriately controlled. On the other hand, when LDL-cholesterol concentrations ≥160 mg/dL occur with multiple (2+) risk factors, long-term (>10-year) risk for CHD is relatively high. Thus, drug therapy deserves consideration. Of course, costs and side effects of drugs must also be taken into account when contemplating lifetime drug therapy.

e. Drug considerations for persons with 0–1 risk factor, 10-year risk <10 percent

The LDL-cholesterol goal in this risk category is <160 mg/dL. For adults with severe elevations of LDL cholesterol (e.g., ≤220 mg/dL), drug therapy can be started simultaneously with TLC. When baseline LDL cholesterol is in the range of 190–219 mg/dL, a 3-month trial of TLC is indicated. If the LDL-cholesterol level remains ≥190 mg/dL after TLC, drug therapy should be considered for most persons. However, if LDL cholesterol falls to the range of 160–189 mg/dL on TLC, drug therapy is optional, depending on clinical judgment. Similarly, if baseline LDL cholesterol is 160–189 mg/dL, a 3-month trial of TLC is indicated; again, if the LDL level persists ≥160 mg/dL on TLC, drug therapy is optional. In either case, factors that favor drug therapy are severe, single risk factors, such as heavy smoking, a family history of premature CHD, very low HDL-cholesterol levels, and the presence of other emerging risk factors (see Section II). Likewise, if triglycerides are high (≥200 mg/dL), non-HDL cholesterol will be a secondary target of therapy.

2. Available drug therapies

a. Overview and general approach

The major classes of drugs for consideration are:

- HMG CoA reductase inhibitors (statins)—lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin
- Bile acid sequestrants—cholestyramine, colestipol, colesevelam
- Nicotinic acid—crystalline, timed-release preparations, Niaspan®

- Fibric acid derivatives (fibrates)—gemfibrozil, fenofibrate, clofibrate

Hormones are also discussed below:

- Estrogen replacement
- Selective estrogen receptor modulators

b. Major drugs

1) HMG CoA reductase inhibitors (statins*)—lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin

These drugs are summarized in Table VI.2–1. The HMG CoA reductase inhibitors are the most effective and practical class of drugs for reducing LDL-cholesterol concentrations. Results from five clinical trials with a mean duration of 5.4 years have documented a decrease in CHD and total mortality, reductions in myocardial infarctions, revascularization procedures, stroke, and peripheral vascular disease (LaRosa et al., 1999; Scandinavian . . . Study Group 1994; Shepherd et al., 1995; Sacks et al., 1996; Downs et al., 1998; Long-Term Intervention . . . Study Group 1998). These trials documented benefits in men and women, in middle-aged and older persons, and in primary and secondary prevention. Approximately 30,000 individuals were randomized to either placebo or statin therapy in these five clinical outcome trials. Statin therapy proved remarkably safe, with no major or unexpected adverse effects observed. Several other types of clinical trials with statin therapy also showed favorable results (Post Coronary Artery Bypass Graft Trial Investigators 1997; Knatterud et al., 2000). Beneficial outcomes in CHD parameters have been reported with almost all of the statins. Thus, statins are highly effective in lowering LDL-cholesterol levels (the primary target of therapy). Statin therapy reduces the risk of essentially every clinical manifestation of the atherosclerotic process; they are easy to administer with good patient acceptance. They have few drug-drug interactions, and they have a good record for safety.

* *Cerivastatin was voluntarily withdrawn from the market by the manufacturer following reports of fatal rhabdomyolysis to the FDA. A substantial proportion of the deaths occurred in patients taking both cerivastatin and gemfibrozil. Rhabdomyolysis associated with cerivastatin use has been reported significantly more frequently than for other statin drugs. Myopathy associated with other statin drugs occurs infrequently, and in most cases, stopping the drug reverses the problem. The significant benefits of statins—lowering cholesterol and reducing the risk for MI and death from CHD—outweigh the risk of developing myopathy or rhabdomyolysis.*

Table VI.2–1. Summary of HMG CoA Reductase Inhibitors

Available Drugs*	Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin
Lipid/lipoprotein effects	LDL cholesterol - ↓ 18–55% HDL cholesterol - ↑ 5–15% Triglycerides - ↓ 7–30%
Major use	To lower LDL cholesterol
Contraindications • **Absolute** • **Relative**	 Active or chronic liver disease Concomitant use of cyclosporine, macrolide antibiotics, various anti-fungal agents and cytochrome P-450 inhibitors (fibrates and nicotinic acid should be used with appropriate caution)
Efficacy	Reduce risk for CHD and stroke
Safety	Side effects minimal in clinical trials
Major side/adverse effects	Myopathy, increased liver transaminases
Usual starting dose	Lovastatin - 20 mg Pravastatin - 20 mg Simvastatin - 20 mg Fluvastatin - 20 mg Atorvastatin - 10 mg
Maximum FDA-approved dose	Lovastatin - 80 mg Pravastatin - 40 mg Simvastatin - 80 mg Fluvastatin - 80 mg Atorvastatin - 80 mg
Available preparations	Lovastatin - 10, 20, 40 mg tablets Pravastatin - 10, 20, 40 mg tablets Simvastatin - 5, 10, 20, 40, 80 mg tablets Fluvastatin - 20, 40, mg capsules, 80 mg XL tablets Atorvastatin - 10, 20, 40, 80 mg tablets

* Cerivastatin was withdrawn from the market by the manufacturer in August, 2001.

Statins inhibit HMG CoA reductase, the rate-limiting step in cholesterol biosynthesis (Endo 1992). This change produces a lowering of LDL-cholesterol levels (Mabuchi et al., 1981; Tobert et al., 1982; Mabuchi et al., 1983; Davignon et al., 1992). Inhibition of cholesterol synthesis reduces hepatic cholesterol content, resulting in increased expression of LDL receptors, which lowers serum LDL-cholesterol levels (Bilheimer et al., 1983). Intermediate density lipoprotein (IDL) and VLDL remnants also are removed via the LDL receptor. The latter effect contributes to lowering of triglyceride-rich lipoproteins (TGRLP) by statins (Vega and Grundy, 1990b; Broyles et al., 1995; Bakker-Arkema et al., 1996). Statins also appear to reduce hepatic release of lipoproteins into the circulation (Arad et al. 1990; 1992); this effect may be due in part to enhanced removal of lipoproteins by LDL receptors within hepatocytes or in the space of Disse (Twisk et al., 2000). In some persons with homozygous familial hypercholesterolemia, high

doses of statins lower LDL-cholesterol levels (Marais et al., 1997; Postiglione et al., 1999; Raal et al., 2000). This latter action is mediated either by increased expression of residual LDL-receptor activity or by inhibition of lipoprotein assembly.

The statins are generally administered with the evening meal or at bedtime. Somewhat greater LDL-cholesterol reductions occur when they are administered at night than in the morning. Most statins have a high first-pass clearance by the liver and a short half-life. Atorvastatin and its metabolites, in contrast, have very long half-lives and thus morning administration is equally effective. Depending upon the specific statin and the dose administered, reductions in LDL cholesterol of 18–55 percent are observed (Jones et al., 1998; Stein 1998). The reductions in LDL cholesterol are dose-dependent and log-linear, so that with each doubling of the dose of statin, LDL-cholesterol levels fall by about 6 percent. HDL cholesterol generally rises by 5–10 percent, but greater increases usually occur in persons with low HDL and elevated triglycerides (LaRosa et al., 1999; Scandinavian . . . Study Group 1994; Shepherd et al., 1995; Sacks et al., 1996; Downs et al., 1998; Long-Term Intervention . . . Study Group 1998; Jones et al., 1998; Stein 1998).

The reductions in triglycerides with the statins generally range from 7–30 percent (LaRosa et al., 1999; Scandinavian . . . Study Group 1994; Shepherd et al., 1995; Sacks et al., 1996; Downs et al., 1998; Long-Term Intervention . . . Study Group 1998; Jones et al., 1998; Stein 1998). In individuals with triglyceride levels of <150 mg/dL, triglyceride responses are inconsistent. But when triglyceride levels are >200 mg/dL, triglycerides fall in direct proportion to LDL-cholesterol lowering (Stein et al., 1998). With very high triglyceride levels, however, LDL-cholesterol lowering is less than that observed with low triglyceride levels. The statins reduce the concentration of all LDL particles, including the small LDL particles, as well as IDL and VLDL remnants (Vega and Grundy, 1990b; Broyles et al., 1995). The combined lowering of LDL and TGRLP with the statins makes them efficacious for reducing non-HDL cholesterol in persons with atherogenic dyslipidemia or combined hyperlipidemias.

The statins are well-tolerated by most persons. Elevated hepatic transaminases generally occur in 0.5–2.0 percent of cases and are dose-dependent (Hsu et al., 1995; Bradford et al., 1991). Bradford et al. (1994) reported that the 2-year incidence of serum transaminase with lovastatin therapy was 0.1 percent for 20 mg/day and 1.9 percent for 80 mg/day. Whether transaminase elevation with statins constitutes true hepatotoxicity has not been determined. In fact, the incidence of clinically important (>3 times upper limit of normal) transaminase elevations in the large statin trials is the same for statin as for placebo. Progression to liver failure is exceedingly rare, if it ever occurs; this observation has led some authorities to conclude that statins do not carry clinically significant hepatotoxicity. Reversal of transaminase elevation is frequently noted with reduction of dose or even continued administration of the same dose. Nonetheless, persons who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in transaminase levels of >3 times upper limit of normal or greater persist, discontinuation of therapy is recommended by the FDA. According to the clinical experience of ATP III panel experts, if the statin has been discontinued, transaminase elevations often do not recur with either rechallenge or selection of another statin (Hunninghake 1990; Cressman et al., 1988). Cholestasis and active liver disease are listed by the

FDA as contraindications to statins. It is not known whether statins worsen the outcome in persons with chronic transaminase elevations due to hepatitis B or C. There is no evidence that they are harmful in patients with fatty liver due to obesity. Their use in persons with various forms of chronic liver disease depends on clinical judgment that balances proven benefit against risk.

That statins can produce myopathy under some circumstances is well established. An elevation of creatine kinase is the best indicator of statin-induced myopathy. Unfortunately, statins have often been discontinued for suspected myopathy which in fact is not present. A common complaint is non-specific muscle aches or joint pains that may be falsely attributed to statin therapy; these symptoms are usually not accompanied by significant increases in creatine kinase. In placebo-controlled trials, the incidence of these complaints is similar between placebo and active drug therapy, suggesting that statins are not responsible in many cases (Bradford et al., 1991). Sometimes, nonetheless, persons can develop clinically significant myopathy, which is characterized by muscle aches, soreness, or weakness, and elevated creatine kinase levels, generally greater than ten times the upper limit of normal. Overall, the incidence of myopathy with elevations in serum creatine kinase during statin therapy is low (Bradford et al., 1994; Insull et al., 2000; Davidson et al., 2000). Failure to recognize myopathy and to discontinue drug therapy can lead to rhabdomyolysis, myoglobinuria, and acute renal necrosis (Pierce et al., 1990). Myopathy is most likely to occur in persons with complex medical problems and/or who are taking multiple medications. Older patients may also be more susceptible. It occurs less frequently with statin monotherapy, but more frequently when statins are used in combination with a variety of medications including cyclosporine, fibrates, macrolide antibiotics, certain anti-fungal drugs, and nicotinic acid (Wanner et al., 1997; Goldman et al., 1989; Hanston and Horn, 1998). Some of the drug-drug interactions involve specific interactions with the cytochrome P-450 drug metabolizing system, especially those involving the 3A4 isozyme (Davidson 2000; Gruer et al., 1999). Routine laboratory monitoring of creatine kinase is of little value in the absence of clinical signs or symptoms. Therefore, all persons started on statins should be instructed to immediately report muscle pain and weakness or brown urine, and a creatine kinase measurement should be done. If myopathy is present or strongly suspected, the statin should be discontinued immediately.

Evidence statements: *HMG CoA reductase inhibitors (statins) are powerful LDL-lowering drugs (A1). Statin therapy reduces risk for acute coronary syndromes, coronary procedures, and other coronary outcomes in both primary and secondary prevention (A1). It also reduces risk for stroke in secondary prevention (A1). Treatment with statins is generally safe, although rarely persons experience myopathy (D1). Myopathy is more likely in persons with complex medical problems or in those who are taking multiple medications (D1).*

Recommendation: *Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.*

2) Bile acid sequestrants—cholestyramine, colestipol, colesevelam

These drugs are summarized in Table VI.2–2. The major action of bile acid sequestrants is to lower LDL cholesterol (Insull et al., 1991; Hunninghake et al., 1995; Superko et al., 1992; Davidson et al., 1999; Lipid Research Clinics Program 1984a). Therapy with cholestyramine reduced the risk of CHD in the Lipid Research Clinics Coronary Primary Prevention Trial (Lipid Research Clinics Program 1984a,b). Beneficial outcomes also occurred in other clinical trials in which sequestrants were combined with other lipid-modifying drugs (Blankenhorn et al., 1987; Brown et al., 1990). Sequestrants add to the LDL-lowering effects of other drugs, notably statins (Lovastatin Study Group III 1988; Pravastatin Multicenter Study Group II 1993; Heinonen et al., 1996). They remain unabsorbed in their passage through the gastrointestinal tract and lack systemic toxicity. Their disadvantages are two-fold. Because of their bulk, they lack convenience of administration; they also cause various gastrointestinal symptoms, notably constipation.

Table VI.2–2. Summary of Bile Acid Sequestrants

Available drugs	Cholestyramine, colestipol, colesevelam
Lipid/lipoprotein effects	LDL cholesterol - ↓ 15–30% HDL cholesterol - ↑ 3–5% Triglycerides - no effect or increase
Major use	To lower LDL cholesterol
Contraindications	
• **Absolute**	Familial dysbetalipoproteinemia Triglycerides >400 mg/dL
• **Relative**	Triglycerides >200 mg/dL
Efficacy	Clinical trial evidence of CHD risk reduction
Safety	Clinical trial evidence of lack of systemic toxicity; GI side effects common
Major side/adverse effects	Upper and lower gastrointestinal complaints common Decrease absorption of other drugs
Usual daily dose	Cholestyramine - 4–16g Colestipol - 5–20g Colesevelam - 2.6–3.8g
Maximum daily dose	Cholestyramine - 24g Colestipol - 30g Colesevelam - 4.4g
Available preparations	Cholestyramine - 9g packets (4g drug) - 378g bulk - 5g packets (4g drug) "light" - 210g bulk Colestipol - 5g packets (5g drug) - 450g bulk Colesevelam - 625 mg tablets

The sequestrants bind bile acids in the intestine through anion exchange; this binding reduces the enterohepatic recirculation of bile acids, which releases feedback regulation on conversion of cholesterol to bile acids in the liver. The resulting decrease in hepatocyte cholesterol content enhances LDL-receptor expression, which in turn lowers serum LDL-cholesterol concentrations (Rudling et al., 1990). In some persons, sequestrants increase hepatic VLDL production (Beil et al., 1982a), thereby raising serum triglyceride levels (Knopp 1999).

Cholestyramine and colestipol are both administered as powders that must be mixed with water or juice. They usually are given once or twice daily with meals. Colestipol also comes in 1g tablets. The LDL-cholesterol-lowering effect of 4g of cholestyramine equals that of 5g of colestipol. Eight to 10 g/day cholestyramine or 10–20 g/day colestipol reduce LDL-cholesterol concentrations by 10–20 percent. Smaller doses of sequestrants (8–10 g/day) generally are well-tolerated; higher doses (16–20 g/day) are less well-tolerated. Colesevelam, a recently marketed drug, is a much more potent bile acid sequestrant. It has been primarily evaluated at doses of 2.6–3.8g/day, and reductions in LDL cholesterol of 12–18 percent are reported (Davidson et al., 1999). Colesevelam is more easily administered and better tolerated than other sequestrants.

Sequestrants add to LDL lowering when combined with other cholesterol-lowering drugs. Whereas doubling the dose of a statin produces only a 6 percent further reduction in LDL cholesterol, adding a moderate dose of a sequestrant to a statin can further lower LDL cholesterol by 12–16 percent (Denke and Grundy, 1995; Knapp et al., 2001; Davidson et al., 2001). Thus, sequestrants are useful in combined drug therapy with statins. Further, sequestrants combined with plant stanol esters apparently enhance LDL lowering (Gylling 1999; Gylling and Miettinen, 1999b). Thus, sequestrants in combination with TLC, including other dietary options for lowering LDL cholesterol (plant stanols/sterols and viscous fiber), should enable many persons to achieve their LDL-cholesterol goal without the need for an agent that is systemically absorbed.

Since sequestrants tend to raise serum triglycerides, they are contraindicated as monotherapy in persons with high triglycerides (>400 mg/dL) and in familial dysbetalipoproteinemia (Crouse 1987). They generally should be used as monotherapy only in persons with triglyceride levels of <200 mg/dL. Bile acid sequestrants are not contradicted in patients with type 2 diabetes (Garg and Grundy, 1994).

Sequestrant therapy can produce a variety of gastrointestinal symptoms, including constipation, abdominal pain, bloating, fullness, nausea, and flatulence (Lipid Research Clinics Program 1984a). These symptoms often can be lessened by moderate doses of standard sequestrants or use of colesevelam. Sequestrants are not absorbed from the intestine, but can decrease the absorption of a number of drugs that are administered concomitantly. The general recommendation is that other drugs should be taken either an hour before or 4 hours after administration of the sequestrant. Colesevelam, which apparently does not decrease absorption of co-administered drugs, need not be administered separately from other drugs.

Evidence statements: *Bile acid sequestrants produce moderate reductions in LDL cholesterol (A1). Sequestrant therapy reduces risk for CHD (A1). They are additive in LDL-cholesterol lowering in combination with other cholesterol-lowering drugs (C1). They lack systemic toxicity (A1).*
Recommendation: *Bile acid sequestrants should be considered as LDL-lowering therapy for persons with moderate elevations in LDL cholesterol, for younger persons with elevated LDL cholesterol, for women with elevated LDL cholesterol who are considering pregnancy, for persons needing only modest reductions in LDL cholesterol to achieve target goals, and for combination therapy with statins in persons with very high LDL-cholesterol levels.*

3) Nicotinic acid

This drug is summarized in Table VI.2–3. Nicotinic acid or niacin favorably affects all lipids and lipoproteins when given in pharmacological doses. Nicotinamide, which is sometimes confused with niacin or nicotinic acid, has only vitamin functions and does not affect lipid and lipoprotein levels. Nicotinic acid lowers serum total and LDL-cholesterol and triglyceride levels and also raises HDL-cholesterol levels. Smaller doses often increase HDL-cholesterol levels, but doses of 2–3 g/day are generally required to produce LDL-cholesterol reductions of 15 percent or greater (Luria 1988; Knopp et al., 1985; Guyton et al., 1998; Guyton et al., 2000; Drood et al., 1991; Vega and Grundy, 1994). Nicotinic acid can also lower Lp(a) up to 30 percent with high doses (Carlson et al., 1989). Whether Lp(a) lowering by nicotinic acid therapy reduces risk for CHD is not known. Nicotinic acid was shown to reduce the risk of recurrent myocardial infarction in the Coronary Drug Project (Coronary Drug Project Research Group 1975), and total mortality was decreased in a 15-year followup of the persons who had originally received nicotinic acid (Canner et al., 1986). Decreased rates of atherosclerotic progression were also observed in three quantitative angiographic trials: FATS (Brown et al., 1990), HATS (Brown BG et al., 2000), and CLAS (Blankenhorn et al., 1987). In all of these trials, nicotinic acid was combined with other LDL-lowering drugs and effects were compared to placebo.

Many crystalline preparations of nicotinic acid are available without a prescription and are inexpensive. Some preparations and a new formulation, Niaspan®, are available by prescription. Niaspan® is a proprietary extended-release formulation of nicotinic acid; its use is associated with less flushing than occurs with usual crystalline preparations.

Table VI.2–3. Summary of Nicotinic Acid

Available drugs	Crystalline nicotinic acid Sustained-release (or timed release) nicotinic acid Extended-release nicotinic acid (Niaspan®)
Lipid/lipoprotein effects	LDL cholesterol - ↓ 5–25% HDL cholesterol - ↑ 15–35% Triglycerides - ↓ 20–50%
Major use	Useful in most lipid and lipoprotein abnormalities
Contraindications • **Absolute** • **Relative**	 Chronic liver disease, severe gout Hyperuricemia; high doses in type 2 diabetes
Efficacy	Clinical trial evidence of CHD risk reduction
Safety	Serious long-term side effects rare for crystalline form; serious hepatotoxicy may be more common with sustained-release form
Major side/adverse effects	Flushing, hyperglycemia, hyperuricemia or gout, upper gastrointestinal distress, hepatotoxicity, especially for sustained-release form
Usual daily dose	Crystalline nicotinic acid - 1.5–3g Sustained-release nicotinic acid - 1–2g Extended-release nicotinic acid (Niaspan®) - 1–2g
Maximum daily dose	Crystalline nicotinic acid - 4.5 g Sustained-release nicotinic acid - 2g Extended-release nicotinic acid (Niaspan®) - 2g
Available preparations	Many OTC preparations by various manufacturers for both crystalline and sustained-release nicotinic acid. The extended-release preparation (Niaspan®) is a prescription drug.

Nicotinic acid appears to alter lipid levels by inhibiting lipoprotein synthesis and decreasing the production of VLDL particles by the liver. It inhibits the peripheral mobilization of free fatty acids, reducing hepatic secretion of VLDL (Langer and Levy, 1971; Grundy et al., 1981). It decreases the plasma concentration of triglyceride, VLDL remnants, and IDL (Martin-Jadraque et al., 1996; Mostaza et al., 1997); and it causes a shift in LDL composition from the small, denser LDL particles to the larger, more buoyant LDL particles (Superko and Krauss, 1992). Nicotinic acid also is the most effective lipid-lowering drug for raising HDL levels (Vega and Grundy, 1994). The changes in HDL cholesterol and triglyceride concentrations tend to be curvilinear (log-linear); thus, smaller doses of nicotinic acid still produce significant increases in HDL or reductions in triglyceride with fewer side effects. The increases in HDL cholesterol are generally in the range of 15–30 percent (Vega and Grundy, 1994), but increases of 40 percent have been noted with very high doses (Luria 1988; Knopp et al., 1985; Knopp et al., 1998; McKenney et al., 1994). The sustained-release preparations usually increase HDL cholesterol

levels by only 10–15 percent (Knopp et al., 1998; McKenney et al., 1994) with the exception of Niaspan® which retains the HDL-raising potential of the crystalline form. Nicotinic acid typically reduces triglyceride levels by 20 to 35 percent, but reductions of 50 percent have been noted with high doses in hypertriglyceridemic persons (Luria 1988; Knopp et al., 1985; Guyton et al., 1998; Guyton et al., 2000; Drood et al., 1991; Vega and Grundy, 1994). Among lipid-lowering agents, nicotinic acid appears to be the most effective for favorably modifying all of the lipoprotein abnormalities associated with atherogenic dyslipidemia.

The degree of LDL-cholesterol lowering by nicotinic acid has varied in different studies. Some studies report little or no change in LDL levels (Vega and Grundy, 1994). However, in one carefully controlled study in patients with hypercholesterolemia (Illingworth et al., 1994), reductions in LDL cholesterol of 5 percent, 16 percent, and 23 percent were noted with daily doses of 1.5, 3.0 and 4.5 grams, respectively. Extended-release nicotinic acid (Niaspan®), which is administered as a single bedtime dose, has been shown to reduce LDL cholesterol by 15 percent at 2 g/day (Guyton et al., 1998; Capuzzi et al., 1998; Guyton et al., 2000; Knopp et al., 1998). Because many persons cannot tolerate higher doses, nicotinic acid is typically not used primarily to lower LDL levels. Instead, it is generally used in combination with other drugs, especially the statins (Guyton and Capuzzi, 1998).

Nicotinic acid therapy can be accompanied by a number of side effects. Flushing of the skin is common with the crystalline form and is intolerable for some persons. However, most persons develop tolerance to the flushing after more prolonged use of the drug. Less severe flushing generally occurs when the drug is taken during or after meals, or if aspirin is administered prior to drug ingestion. A newer preparation, Niaspan®, is reported to cause less flushing than crystalline nicotinic acid. A variety of gastrointestinal symptoms, including nausea, dyspepsia, flatulence, vomiting, diarrhea, and activation of peptic ulcer may occur. Three other major adverse effects include hepatotoxicity, hyperuricemia and gout, and hyperglycemia. The risk of all three is increased with higher doses, especially at doses of 2 g or higher. The risk of hepatotoxicity appears to be greater with the sustained-release preparations, although not with Niaspan®. Impending hepatotoxicity should be considered if there is a dramatic reduction in plasma lipids (Tato et al., 1998). Nicotinic acid reduces insulin sensitivity, and higher doses (>3 g per day) often worsen hyperglycemia in persons with type 2 diabetes (Garg and Grundy, 1990). Recent studies suggest that lower doses do not unduly worsen hyperglycemia (Elam et al., 2000; Grundy et al., 2001b). Other adverse effects include conjunctivitis, nasal stuffiness, acanthosis nigricans, ichthyosis, and retinal edema (toxic amblyopia).

Nicotinic acid is usually administered in two or three doses a day, with the exception of Niaspan®, which is administered as a single dose at bedtime. Crystalline nicotinic acid is the least expensive drug, and small doses are especially useful for increasing HDL-cholesterol levels or lowering triglycerides. The timed-release (sustained-release) preparations are designed to minimize cutaneous flushing. When switching from crystalline nicotinic acid to a sustained-release preparation, smaller doses should be used to reduce the risk of hepatotoxicity. The dose can then be carefully titrated upward, generally to a level not exceeding 2 g/day. Rare cases of fulminant hepatitis have been reported with sustained-release preparations (Mullin et al., 1989; Etchason et al., 1991; Rader et al., 1992). Considerable variation exists among different sustained-release preparations, and persons should be advised not to switch from one preparation

to another. Niaspan® is an extended-release preparation; however, its more rapid-release than sustained-release preparation appears to reduce the risk of hepatotoxicity. Niaspan® also is associated with less flushing than with crystalline nicotinic acid. Since many nicotinic acid preparations are available without a prescription, persons should be instructed that nicotinic acid is associated with many severe adverse effects and regular monitoring by a health professional is essential.

Although nicotinic acid can be highly efficacious and favorably modify the lipoprotein profile, especially in patients with atherogenic dyslipidemia, its long-term use is limited for many patients by side effects (Gibbons et al., 1995). For this reason, the drug is generally reserved for patients at higher short-term risk, i.e., for those with CHD, CHD risk equivalents, or multiple (2+) risk factors with 10-year risk for CHD of 10–20 percent. Its use for long-term prevention of CHD in persons with 10-year risk <10 percent is not well established, and in such persons, should be used more cautiously. For example, it is not known whether long-term use of nicotinic acid for lower-risk persons with isolated low HDL cholesterol is beneficial.

Evidence statements: *Nicotinic acid effectively modifies atherogenic dyslipidemia by reducing TGRLP, raising HDL cholesterol, and transforming small LDL into normal-sized LDL (C1). Among lipid-lowering agents, nicotinic acid is the most effective HDL-raising drug (C1). Nicotinic acid usually causes a moderate reduction in LDL-cholesterol levels (C1), and it is the most effective drug for reducing Lp(a) levels (C1).*
Evidence statements: *Nicotinic acid therapy is commonly accompanied by a variety of side effects, including flushing and itching of the skin, gastrointestinal distress, glucose intolerance, hepatotoxicity, hyperuricemia, and other rarer side effects (C1). Hepatotoxicity is more common with sustained-release preparations (D1).*
Evidence statement: *Nicotinic acid therapy produces a moderate reduction in CHD risk, either when used alone or in combination with other lipid-lowering drugs (A2, B2).*
Recommendation: *Nicotinic acid should be considered as a therapeutic option for higher-risk persons with atherogenic dyslipidemia. It should be considered as a single agent in higher-risk persons with atherogenic dyslipidemia who do not have a substantial increase in LDL-cholesterol levels, and in combination therapy with other cholesterol-lowering drugs in higher-risk persons with atherogenic dyslipidemia combined with elevated LDL-cholesterol levels.*
Recommendation: *Nicotinic acid should be used with caution in persons with active liver disease, recent peptic ulcer, hyperuricemia and gout, and type 2 diabetes. High doses of nicotinic acid (>3 g per day) generally should be avoided in persons with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia.*

4) Fibric acid derivatives (fibrates): gemfibrozil, fenofibrate, clofibrate

These drugs are summarized in Table VI.2–4. There are three fibrates—gemfibrozil, fenofibrate, and clofibrate—currently available in the United States. Other fibrate preparations, including

bezafibrate and ciprofibrate, are available outside the United States. The fibrates are primarily used for lowering triglycerides because the LDL-cholesterol-lowering effects of gemfibrozil and clofibrate are generally in the range of 10 percent or less in persons with primary hypercholesterolemia. Only slight changes in LDL cholesterol are noted in persons with combined hyperlipidemia, and LDL-cholesterol levels generally rise on fibrate therapy in persons with hypertriglyceridemia (Leaf et al., 1989; Pauciullo et al., 1990). Fenofibrate frequently reduces LDL-cholesterol levels by 15 to 20 percent when triglycerides are not elevated; other fibrates not available in the United States are also more effective in lowering LDL cholesterol (Kornitzer et al., 1994; Gavish et al., 1986; Illingworth et al., 1982). Therapy with clofibrate and gemfibrozil reduced risk of fatal and non-fatal myocardial infarction in two large primary prevention trials (Committee of Principal Investigators 1978; Frick et al., 1987), and gemfibrozil therapy reduced CHD death and non-fatal myocardial infarction and stroke in a recently reported secondary prevention trial (Rubins et al., 1999). However, this beneficial effect on cardiovascular outcomes has not been observed in all large fibrate trials (Coronary Drug Project Research Group 1975; Bezafibrate Infarction Prevention Study 2000).

Table VI.2–4. Summary of Fibric-Acid Derivatives

Available drugs	Gemfibrozil, fenofibrate, clofibrate
Lipid/lipoprotein effects	LDL cholesterol - ↓ 5–20% (in nonhypertriglyceridemic persons); may be increased in hypertriglyceridemic persons HDL cholesterol - ↑ 10–35% (more in severe hypertriglyceridemia) Triglycerides - ↓ 20–50%
Major uses	Hypertriglyceridemia, atherogenic dyslipidemia
Contraindications	Severe hepatic or renal insufficiency
Efficacy	Clinical trials indicate a moderate reduction in CHD risk
Safety	Serious side effects seemingly do not occur in the long term, although early studies suggested an increase in non-CHD mortality
Major side/adverse effects	Dyspepsia, various upper gastrointestinal complaints, cholesterol gallstones, myopathy
Usual daily dose	Gemfibrozil - 600 mg bid Fenofibrate - 200 mg daily Clofibrate - 1000 mg bid
Maximum daily dose	Gemfibrozil - 1200 mg Fenofibrate - 200 mg Clofibrate - 2000 mg
Available preparations	Gemfibrozil - 600 mg tablets Fenofibrate - 67 and 200 mg tablets Clofibrate - 500 mg capsules

There has been some concern about the short-term safety of the fibrates. Although nonfatal myocardial infarction fell by 25 percent in the WHO Clofibrate Study, a primary prevention

study, total mortality was significantly higher in the clofibrate group, due to an increase in non-CHD deaths (Committee of Principal Investigators 1978). The use of clofibrate in general medical practice decreased markedly after this study. The Helsinki Heart Study, a primary prevention trial employing gemfibrozil, demonstrated a 37 percent reduction in fatal and non-fatal myocardial infarctions and no change in total mortality during the course of the study (Frick et al., 1987). After 8.5–10 years of followup, non-cardiac death and all cause mortality were numerically higher in the group that had received gemfibrozil during the study (Huttunen et al., 1994). However, this increase was *not* statistically significant. Moreover, after 10 years of followup, no difference in cancer rates was observed between those who had received gemfibrozil or placebo. In the Veterans Administration HDL Intervention Trial (VA-HIT) (Rubins et al., 1999), a secondary prevention trial, gemfibrozil therapy reduced risk for CHD death and nonfatal myocardial infarction by 22 percent; stroke rates also were reduced by gemfibrozil therapy. In this study, there was no suggestion of an increased risk of non-CHD mortality. Neither was there an increase in non-CHD mortality from fibrate therapy in the recently reported Bezafibrate Infarction Prevention (BIP) study (Bezafibrate Infarction Prevention Study 2000). Furthermore, worldwide clinical experience with various fibrates is vast. No evidence of specific toxicity that enhances non-CHD mortality has emerged. This experience, taken in the light of all the clinical trials, provides little support for the concern that fibrates carry significant short-term toxicity that precludes their use for appropriately selected persons.

The mechanism of action of the fibrates is complex and there may be some variation among the drugs in this class. Recent research shows fibrates to be agonists for the nuclear transcription factor *peroxisome proliferator activated receptor-alpha (PPAR-alpha)* (Schoonjans et al., 1996). Through this mechanism, fibrates downregulate the apolipoprotein CIII gene and upregulate genes for apolipoprotein A-1, fatty acid transport protein, fatty acid oxidation, and possibly lipoprotein lipase (Fruchart et al., 1998). Its effects on lipoprotein lipase and apolipoprotein CIII (an inhibitor of lipoprotein lipase) enhance the catabolism of TGRLP, whereas increased fatty acid oxidation reduces formation of VLDL triglycerides. These effects account for serum triglyceride lowering, which is the major action of fibrates. Serum triglyceride lowering combined with increased synthesis of apolipoprotein AI and AII tend to raise HDL-cholesterol levels (Vu-Dac et al., 1995). Triglyceride lowering also transforms small, dense LDL into normal-sized LDL (Eisenberg et al., 1984). The effect of PPAR activity on other atherogenic mechanisms is now being evaluated (Pineda Torra et al., 1999; Neve et al., 2000).

The fibrates typically reduce triglyceride by 25–50 percent; the greater reductions generally occur in severely hypertriglyceridemic individuals (Leaf et al., 1989). Fibrates usually raise HDL cholesterol by 10–15 percent, but greater increases can occur in persons with very high triglyceride levels and very low HDL-cholesterol levels. Thus fibrates, like nicotinic acid, primarily target atherogenic dyslipidemia. In addition, the ability of fibrates to lower triglycerides has led to their wide usage in persons having very high triglyceride levels and chylomicronemia (Leaf et al., 1989). The purpose of fibrate therapy in such persons is to reduce the risk for acute pancreatitis. Their value for this purpose is well recognized. Finally, fibrates are highly effective for reducing beta-VLDL concentrations in persons with dysbetalipoproteinemia (Mahley and Rall, 1995).

Whether fibrate modification of atherogenic dyslipidemia reduces risk for CHD is an important issue. Results of clinical trials with fibrates are summarized in Table II.3–1. The major primary prevention trials were the WHO clofibrate trial and the Helsinki Heart Study gemfibrozil trial (Committee of Principal Investigators 1978; Frick et al., 1987). In both trials, CHD incidence was significantly reduced by fibrate therapy. Early secondary prevention trials with clofibrate therapy gave suggestive evidence of CHD risk reduction. In another secondary prevention trial, the Coronary Drug Project, clofibrate therapy failed to significantly reduce risk for CHD (Coronary Drug Project Research Group 1975). Likewise, in the BIP trial, bezafibrate therapy did not significantly reduce recurrent major coronary events in persons with established CHD (Bezafibrate Infarction Prevention Study 2000). In contrast, gemfibrozil therapy in the VA-HIT trial showed wide benefit by significantly reducing CHD events and strokes in persons with established CHD (Table II.3–1 and Table II.6–3). Thus, taken as a whole, clinical trials of fibrate therapy strongly suggest a reduction in CHD incidence, although results are less robust than with statin therapy. Further, a reduction in total mortality, which would have required a greater reduction in CHD mortality than observed, has not been demonstrated with fibrate therapy (see Table II.9–1). This failure does not rule out a benefit of fibrate therapy but certainly suggests less efficacy than with statin therapy.

Several studies have employed fibrates in combination with LDL-lowering drugs in persons with combined hyperlipidemia (elevated LDL + atherogenic dyslipidemia). Combination therapy improves the overall lipoprotein profile compared to either fibrates or LDL-lowering drugs alone. This finding has led to a movement for considering use of fibrates in combination with statins in high-risk individuals whose triglyceride levels are still elevated. In some persons, this combination may better achieve the secondary target for non-HDL cholesterol than will statins alone. Nonetheless, to date no clinical trials have been published that compare statins vs. statins + fibrates on CHD outcomes.

The fibrates are generally well-tolerated in most persons. Gastrointestinal complaints are the most common complaints. All drugs in this class appear to increase the lithogenicity of bile, increasing the likelihood of cholesterol gallstones (Palmer 1987). A portion of the excess deaths reported in the WHO Clofibrate Study was related to gallstone disease (Coronary Drug Project Research Group 1977). The fibrates bind strongly to serum albumin and so may displace other drugs that bind with albumin. For example, fibrates displace warfarin from its albumin-binding sites, thereby increasing the latter's anticoagulant effect. Fibrates are excreted primarily by the kidney; consequently, elevated serum levels occur in persons with renal failure and risk for myopathy is greatly increased. The combination of fibrate with a statin also increases the risk for myopathy, which can lead to rhabdomyolysis (Pierce et al., 1990; Duell et al., 1998). None of these well-established side effects can account for the increased total mortality observed in the WHO clofibrate study (Report of the Committee of Principal Investigators 1980; 1984). The increase in non-CHD deaths remains unexplained. An increase in non-CHD mortality has not been confirmed by subsequent trials with fibrate therapy.

Evidence statements: *Fibrates are effective for modifying atherogenic dyslipidemia, and particularly for lowering serum triglycerides (C1). They produce moderate elevations of HDL cholesterol (C1). Fibrates also are effective for treatment of dysbetalipoproteinemia (elevated beta-VLDL) (C1). They also can produce some lowering of LDL, the degree of which may vary among different fibrate preparations (C1). Fibrates also can be combined with LDL-lowering drugs in treatment of combined hyperlipidemia to improve the lipoprotein profile, although there is no clinical-trial evidence of efficacy for CHD risk reduction with combined drug therapy (C1, D1).*
Evidence statements: *Fibrate therapy moderately reduces risk for CHD (A2, B1). It may also reduce risk for stroke in secondary prevention (A2).*
Evidence statements: *Evidence for an increase in total mortality due to an increased non-CHD mortality, observed in the first large primary prevention trial with clofibrate, has not been substantiated in subsequent primary or secondary prevention trials with other fibrates (gemfibrozil or bezafibrate) (A2, B1). Nonetheless, fibrates have the potential to produce some side effects. Fibrate therapy alone carries an increased risk for cholesterol gallstones (A2), and the combination of fibrate and statin imparts an increased risk for myopathy (B2).*
Recommendations: *Fibrates can be recommended for persons with very high triglycerides to reduce risk for acute pancreatitis. They also can be recommended for persons with dysbetalipoproteinemia (elevated beta-VLDL). Fibrate therapy should be considered an option for treatment of persons with established CHD who have low levels of LDL cholesterol and atherogenic dyslipidemia. They also should be considered in combination with statin therapy in persons who have elevated LDL cholesterol and atherogenic dyslipidemia.*

c. Other drugs

Probucol is no longer available in the United States and in most other countries. This drug has powerful antioxidant properties, which is theoretically beneficial. In one angiographic trial, probucol therapy failed to retard femoral atherogenesis; neither was a reduction in CHD risk observed. There is some current interest in reports that probucol reduced the restenosis rates following angioplasty (Tardif et al., 1997; Rodes et al., 1998).

d. n-3 fatty acids

n-3 fatty acids (linolenic acid, DHA, and EPA) have two potential uses. In higher doses, DHA and EPA lower serum triglycerides by reducing hepatic secretion of triglyceride-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. They are available in capsules of fish oil, and doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia.

Recent clinical trials also suggest that relatively high intakes of n-3 fatty acids (1–2 g/day) in the form of fish, fish oils, or high-linolenic acid oils will reduce risk for major coronary events in persons with established CHD (see Section V.3.c). Although this usage falls outside the realm of

"cholesterol management," the ATP III panel recognizes that n-3 fatty acids can be a therapeutic option in secondary prevention. The n-3 fatty acids are recommended only as an option because the strength of the clinical trial evidence is moderate at present. The n-3 fatty acids can be derived from either foods (n-3 rich vegetable oils or fatty fish) or from fish-oil supplements. In the view of the ATP III panel, more definitive clinical trials are required before relatively high intakes of n-3 fatty acids (1–2 g/day) can be strongly recommended for either primary or secondary prevention.

e. Hormone replacement therapy (HRT)

Risk for CHD is increased in postmenopausal women whether the menopause is natural, surgical, or premature (Kannel et al., 1976; Rosenberg et al., 1981; Colditz et al., 1987). Loss of estrogen has been proposed as a cause for increased risk. This putative mechanism was strengthened by results of numerous case-control and epidemiological studies which suggested that either estrogen alone, or in combination with progestin, reduces risk for CHD in primary and secondary prevention. However, benefit of estrogen replacement was not confirmed in a secondary prevention trial, the Heart and Estrogen/progestin Replacement Study (HERS) (Hulley et al., 1998). A subsequent angiographic study also revealed no apparent benefit from HRT (Herrington et al., 2000). The major features of the HERS trial are shown in Table VI.2–5.

Table VI.2–5. Major Characteristics and Outcomes of HERS Trial

Patient Characteristics	Study Design	Clinical Outcomes (E+P vs. Placebo)	Side Effects
2,763 postmenopausal women	Randomized, double-blind	CHD events 172 vs. 176	Thromboembolic events (E+P $\geq$ placebo)
Age <80 years (mean age 67 years)	Placebo vs. 0.625 mg of conjugated equine estrogens and 2.5 mg medroxyprogesterone acetate (E+P)	CHD death 71 vs. 58	Gallbladder disease (E+P $\geq$ placebo)
History of CHD	Duration: 4.1 years	Non-fatal MI 116 vs. 129	
Absent hysterectomy			
BMI >27 kg/m^2			
45% on lipid-lowering drugs at entry			

As shown in the table, estrogen/progestin replacement produced no overall benefit for the entire duration of the trial. Moreover, both CHD death and non-fatal myocardial infarction were increased, especially during the first year. Estrogen/progestin (E+P) replacement increased risk for thromboembolic events and caused more gallbladder disease (Hulley et al., 1998; Grady et al., 2000). Thus, E+P produced no overall benefit for the entire study and increased risk for CHD events, thromboembolic events, and gallbladder disease in the early phase of the trial. There was a suggestion, however, that E+P reduced non-fatal myocardial infarction in the latter

years of the trial. A 3-year followup study is currently in progress. The overall interpretation of the trial by the investigators was that HRT should not be initiated in postmenopausal women with CHD for the purpose of reducing risk of CHD, but if women had already been on HRT for a period of time, they could continue, with the expectation that there may be some later benefit. The mechanism for the early increase in CHD events and increased thromboembolic events has not been clearly defined, but it appears that E+P administration was associated with a prothrombotic tendency.

Estrogen therapy favorably influences lipid and lipoprotein levels, but this did not translate into a reduction in CHD risk in the HERS trial. In postmenopausal women, orally administered estrogen preparations (0.625 mg of conjugated estrogen or 2 mg of micronized estradiol) reduce LDL-cholesterol levels by 10–15 percent and increase HDL-cholesterol levels up to 15 percent (Cauley et al., 1983; Jensen et al., 1986; Granfone et al., 1992). Co-administration of progestin may decrease the HDL-cholesterol-raising effect of estrogen. In the HERS trial, the mean difference between E+P minus placebo was an 11 percent decrease in LDL cholesterol, a 10 percent increase in HDL cholesterol and an 8 percent increase in triglycerides.

There is no definitive explanation for why the epidemiologic/observational studies provided markedly different results from the HERS trial. The HERS trial clearly demonstrates the need for controlled clinical trials. Some investigators postulate that if lower doses of estrogen, different progestins, younger age group, estrogen only, or women without CHD had been employed, the results may have been different. The NHLBI Women's Health Initiative is utilizing the same hormonal preparation in a wide range of ages in an estrogen-only and in an estrogen/progestin group in women without CHD (Women's Health Initiative Study Group 1998). This trial may answer some of the questions, but the results will probably not be available before 2003. There is also a possibility of an increased risk of breast cancer with prolonged HRT (Colditz et al., 1993; Steinberg et al., 1994; Barrett-Connor and Grady, 1998; Torgerson 2000; Collaborative Group on Hormonal Factors in Breast Cancer 1997).

Evidence statements: *Hormone replacement therapy in postmenopausal women does not reduce risk for major CHD events or coronary deaths in secondary prevention (A2). Moreover, hormone replacement therapy carries an increased risk for thromboembolism and gallbladder disease (A2).*
Recommendation: *Hormonal replacement therapy cannot be recommended for the express purpose of preventing CHD. Instead, control of risk factors should be the primary approach to reducing CHD risk in women. There may be other valid reasons for hormonal replacement therapy, such as for management of perimenopausal and postmenopausal symptoms or for treatment or prevention of osteoporosis.*

1) Selective estrogen receptor modulators (SERM)—Raloxifene

A number of SERMs are under development. Raloxifene imparts benefits similar to those of HRT on bone density in postmenopausal women. Raloxifene also has an LDL-cholesterol-lowering effect similar to that of estrogen, but the HDL-raising effect appears to be less (Walsh

et al., 1998). Clinical trials to evaluate its effect on CHD risk are underway. Again, until controlled clinical trials are available that demonstrate a reduction in CHD risk, this class of drugs should not be considered for the purpose of CHD prevention. SERMs also increase the risk of thromboembolic events.

f. Miscellaneous drugs and therapeutic approaches

1) Investigational drugs

Many new cholesterol-lowering drugs with a wide range of mechanistic actions are currently in various phases of development. It is still too early to predict which drugs will be approved by the FDA and what their long-term toxicities may be. They will also have the near-term disadvantage of lacking clinical trials documenting a reduction in CHD clinical events.

2) Other approaches

With the advent of statins, effective control of LDL-cholesterol levels can now be achieved in the majority of persons with either monotherapy or drug combinations. Persons with severe forms of hypercholesterolemia or other hyperlipidemias who cannot be adequately controlled should be referred to a center specializing in lipid disorders. LDL apheresis is now available for persons with very high LDL levels, but the procedure is costly and time-consuming. The FDA recently approved two commercial techniques for this purpose: (1) a heparin-induced extracorporeal lipoprotein precipitation, and (2) a dextran sulfate cellulose adsorbent for removal of lipoproteins.

3. Selection of drugs for elevated LDL cholesterol

Reduction in serum concentrations of LDL cholesterol is the primary approach to lowering the risk of CHD in both primary and secondary prevention. In persons whose triglycerides are elevated along with LDL cholesterol, it may also be desirable to lower triglycerides and increase HDL-cholesterol concentrations. Several factors influence the selection of initial drug therapy in individual persons. These include the lipoprotein profile and magnitude of change needed to attain goals of therapy, concurrent drug therapies that may increase the risk of side effects with specific drugs, and the presence of other medical disorders that may influence drug metabolism or be adversely influenced by a specific hypolipidemic drug.

Statins are the most effective class of drugs for reducing LDL-cholesterol concentrations: they are well tolerated, easy to administer, and they are usually the first drugs used. Five statins (lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin) are approved for clinical use in the United States[*]. Available statins differ somewhat in the degree of LDL-cholesterol lowering that can be achieved per mg dose. In addition, the metabolic clearance of these drugs also vary. Simvastatin and lovastatins undergo metabolic inactivation by the 3A4 isozyme of cytochrome p-450 (CYP 3A4); atorvastatin is also a substrate for CYP 3Y4, though some of its metabolites

[*] *Cerivastatin was withdrawn from the market by the manufacturer in August, 2001.*

remain active; and fluvastatin is metabolized by CYP 2C9. Pravastatin appears not to be metabolized by the p-450 system. These differences can have implications for drug-drug interactions, particularly where the concern is myopathy related to elevated systemic levels of the statin. Statins vary in the dose required to produce a given degree of LDL lowering. Whether different doses that produce the same degree of LDL lowering differ in side effect profiles is unknown because of a lack of direct comparison studies. For all statins, the incidence of side effects increases with higher doses. The degree of LDL lowering that is required to achieve target goals and the percent of LDL lowering that is seen with the usual starting dose and maximum dose of the statins are illustrated in Table VI.3–1. In general, for every doubling of the dose of a statin, LDL levels fall by approximately 6 percent.

The dose of statin required to achieve target goals can be extrapolated from Table VI.3–1. However, the response of an individual may vary considerably and cannot be predicted. The LDL response may be influenced by a number of factors, including diet and drug compliance, the genetic cause of hypercholesterolemia, gender and hormonal status, apoE phenotype, and differences in drug absorption and metabolism. There is a tendency in current clinical practice to initiate therapy with the usual starting dose, but the dose often is not titrated upwards to achieve target goals. Persons requiring large LDL reductions will never achieve target goals with the starting dose of some statins. Since the absolute incidence rates of side effects are not much greater at higher doses of currently available preparations, persons requiring major LDL-cholesterol lowering should be started on doses (or their equivalents) used in most clinical trials. Doses can then be increased as needed to achieve the recommended LDL goal. Alternatively, a second LDL-lowering drug (e.g., bile acid sequestrant or nicotinic acid) can be added to standard doses of statin.

The bile acid sequestrants are the second most effective class of drugs for lowering LDL-cholesterol levels. They are particularly useful in combination with statins to achieve major reductions in LDL-cholesterol levels. They can either be added to a statin when maximal doses of statin have not achieved target goals, or they can be added to lower doses of statin if there are concerns about the tolerability and side effects of higher doses. Cholestyramine (8–16 g/day) or colestipol (10–20 g/day) usually produce 10–20 percent reductions in LDL cholesterol when administered as monotherapy, and colesevelam lowers LDL cholesterol by 12–18 percent. Similar reductions in LDL cholesterol are noted when the sequestrants are added to low doses of statins, but the additional LDL-cholesterol lowering is less when added to statins given at higher doses. For purposes of drug safety, bile acid sequestrants can be considered as monotherapy in younger persons, women considering pregnancy, and when only modest LDL lowering is needed.

The LDL-cholesterol-lowering effects of nicotinic acid are usually modest and can be quite variable. Reductions in LDL of 5–23 percent have been noted with doses of 1.5 to 4.5 g of crystalline nicotinic acid and 10–20 percent at 2.0 to 3.0 g of Niaspan® (Capuzzi et al., 1998; Guyton et al., 2000; Goldberg et al., 2000; Morgan et al., 1996). Nicotinic acid should be considered if additional LDL-cholesterol lowering is required after statin administration, especially in persons who do not tolerate sequestrants or who prefer to take medication in tablet form. Nicotinic acid is also considered if, in addition to LDL-cholesterol lowering, increases in HDL cholesterol and decreases in triglycerides and Lp(a) are needed.

The fibrates usually do not significantly enhance LDL-cholesterol lowering when added to a statin. However, if a patient is not at LDL target level and has not tolerated a bile acid sequestrant or nicotinic acid, addition of fenofibrate may enhance LDL lowering in some patients (Kiortisis et al., 2000); it may also be useful if the patient has concomitant atherogenic dyslipidemia (Ellen and McPherson, 1998).

Table VI.3–1. Achieving Target LDL-Cholesterol (LDL-C) Goals

Baseline LDL-C	130	160	190	220
(Percent Reduction to Achieve Target Goals)				
Target LDL-C <100	23	38	47	55
Target LDL-C <130	—	19	32	41
Target LDL-C <160	—	—	16	27

Average Percent Reduction in LDL Cholesterol With Usual Starting Dose and Maximal Statin Dose*

		Starting Dose	Maximum Dose
Lovastatin	20, 80 mg	24	40†
Pravastatin	20, 40 mg	24	34†
Simvastatin	20, 80 mg	35	46
Fluvastatin	20, 80 mg	18	31
Atorvastatin	10, 80 mg	37	57

* Maximum dose currently approved by the FDA.

† Administered in divided doses.

The use of drugs for treatment of other forms of dyslipidemia (severe hypercholesterolemias, isolated low HDL, hypertriglyceridemias, diabetic dyslipidemia, and other secondary forms of hyperlipidemia) are considered in Section VII.

a. Practical advice on combined drug therapy

Some persons will require combined drug therapy to reach ATP III treatment goals. Combination therapy may be needed to provide additional reduction of LDL cholesterol, to achieve the goal for non-HDL cholesterol, to treat severe hypertriglyceridemia, and if it seems advisable, to raise HDL-cholesterol levels. Although it seems desirable to improve the overall lipoprotein profile with combined drug therapy, major randomized controlled trials have not been carried out to test for efficacy and safety in large numbers of persons. Nonetheless, several smaller trials and angiographic trials have provided evidence of positive benefit from combined drug therapy.

1) Statin—bile acid sequestrant combination

In the majority of persons who are treated with a statin, the LDL-cholesterol goal can be reached. However, in persons with severe polygenic or familial hypercholesterolemia, a statin alone may

not be enough. In these cases, combination therapy with a bile acid sequestrant or nicotinic acid added to the statin, or a sequestrant-nicotinic acid combination, should be considered for additional LDL-cholesterol lowering. Of these, the statin-sequestrant combination may be the most effective, reducing LDL cholesterol by as much as 70 percent. The alternative combinations are generally less effective.

Following are practical considerations when utilizing statins and sequestrants in combination.

- The dose of the sequestrant in the statin-sequestrant combination can be low or moderate. Higher doses do not appear to add signficiantly to LDL-cholesterol-lowering efficacy (Leren et al., 1988; Sprecher et al., 1994; Pan et al., 1990).
- Since the statin-sequestrant combination may more effectively lower LDL than a maximum dose of statin, consideration should be given to use of a combination approach early in the course of treating persons with very high LDL-cholesterol levels (Pan et al., 1990; Denke and Grundy, 1995).
- The LDL-cholesterol lowering achieved with the statin-sequestrant combination appears to have a ceiling beyond which there is little if any additional LDL lowering even if the statin or sequestrant doses are further increased. In these cases, consideration can be given to adding a third agent, such as nicotinic acid. Bile acid sequestrants will reduce the bioavailability, but not the LDL-lowering action, of the statin when administered together. Thus, the drugs may be given together. However, it is probably best to give the statin at night (bedtime) and the sequestrant with each meal. It is not necessary to separate the time of administration of colesevelam and statins.
- If the statin-sequestrant combination is not successful in achieving the LDL-cholesterol goal, addition of nicotinic acid to the combination can be considered (Brown et al., 1997). Studies have shown that the use of Niaspan® provides equivalent effect on lipid parameters and is better tolerated than immediate release of nicotinic acid (Rader et al., 1992).

2) Statin—fibrate combination therapy

The combination of statins and fibrates has proven to be highly effective for improvement of the lipoprotein profile in patients with combined hyperlipidemia (East et al., 1988; Athyros et al., 1997; Yeshrun et al., 1993; Ellen and McPherson, 1998). It also may be useful for patients with elevated LDL cholesterol and atherogenic dyslipidemia. A statin + fibrate can reduce both LDL cholesterol and VLDL cholesterol (i.e., non-HDL cholesterol) in patients with elevated triglycerides. Since the primary aim of cholesterol management is LDL reduction, statin therapy usually will be introduced before fibrates. In some patients with high triglycerides, both LDL and non-HDL goals can be attained with higher doses of statins. However, an alternative approach is to use a statin + fibrate. To date no clinical trials have been carried out in patients with hypertriglyceridemia to document the relative value of these two approaches.

The major concern about this combination is the potential for occurrence of myopathy. In the past, this combination was widely thought to be “contraindicated” because of the potential danger of myopathy. More recently, statin-fibrate combination therapy has been used with apparent safety in the majority of persons. It should be noted that the specific combination of

cerivastatin and gemfibrozil caused more clinical myopathy than is noted with other statin drugs. This is one factor that led to the voluntary withdrawl of cerivastatin from the market. Several key points must be kept in mind when using statin-fibrate combination therapy.

- Ensure that the patient has normal renal function.
- Ensure that there are no potential drug interactions that could increase the systemic blood levels of either the statin or fibrate.
- Limit the initial dose of the statin to a starting or intermediate dose when combining it with a fibrate. The dose of statin can then be increased cautiously.
- Teach the patient to recognize and report symptoms of muscle soreness, tenderness, and pain.
- Obtain a creatine kinase (CK) blood level prior to beginning combination therapy to document the patient's baseline level. Repeat this measurement if the patient reports muscle symptoms suggestive of myopathy.
- If the patient experiences muscle soreness, tenderness, or pain, with or without CK elevations, rule out common causes such as exercise or strenuous work. Advise moderation in activity for persons who experience this finding during combination therapy.
- Discontinue combination therapy if a CK greater than ten times the upper limit of normal (ULN) is encountered in a patient with muscle soreness, tenderness, or pain. Wait for symptoms to vanish and CK levels to return to normal before reinitiating therapy with either drug and use a lower dose of the drug(s).

If the patient experiences muscle soreness, tenderness, or pain with either no CK elevation or a moderate elevation (i.e., between three and ten times the upper limit of normal), monitor the patient's symptoms and CK levels until symptoms resolve and the CK returns to normal or until the clinical situation worsens to the point described above, mandating discontinuation of therapy. Following are summary comments reflecting current experience with these issues.

- Although not consistent in the literature, the general terminology used to describe muscle toxicity with these agents includes *myalgia* to reflect muscle symptoms without CK elevations, *myositis* for increased CK levels without muscle symptoms, and *myopathy* for muscle symptoms with CK elevations. Severe myopathy (*rhabdomyolysis*) may subsequently occur. Technically, all of these terms fall under the category of *myopathy.*
- Statin therapy appears to carry a small but definite risk of myopathy when used alone. According to several large databases, the incidence of myopathy is reported to be 0.08 percent with lovastatin and simvastatin (Bradford et al., 1991; Hunninghake 1990; Boccuzzi et al., 1991). Elevations of CK greater than ten times the ULN have been reported in 0.09 percent of persons treated with pravastatin. All currently marketed statins appear to have a similar potential for causing this adverse effect.
- Fibrate treatment alone appears to be associated with some risk of muscle toxicity, although probably less than that of statins.
- Of the nearly 600 persons who have participated in controlled clinical trials of a statin and fibrate combination, 1 percent have experienced a CK greater than three times ULN

without muscle symptoms and 1 percent have been withdrawn from therapy because of muscle pain (Shepherd 1995; Ellen and McPherson, 1998; Rosenson and Frauenheim, 1994; Murdock et al., 1999; Iliadis and Rosenson, 1999; Zambon et al., 1999; Napoli et al., 1997; Farnier and Dejager, 2000). None of these events were considered serious. No cases of rhabdomyolysis or myoglobinuria have been encountered in these clinical trials. The experience in these trials is predominantly with lovastatin and gemfibrozil. Other statin-fibrate combinations may well give similar results. A prior report from FDA surveillance of a 30 percent incidence of myopathy associated with a statin-fibrate combination and a 5 percent incidence of myopathy associated with a statin-nicotinic acid combination appears to be a gross overestimate of the problem (Pierce et al., 1990).

3) Statin—nicotinic acid combination therapy

This combination is attractive because of the favorable effects of nicotinic acid on atherogenic dyslipidemia. Combining the powerful LDL-lowering action of statins with the triglyceride-lowering and HDL-raising actions of nicotinic acid offers the potential to correct most forms of complex dyslipidemias. The relative inexpensiveness of nicotinic acid also makes for an attractive combination. Several small-scale clinical trials speak to the efficacy of this combination for modifying an abnormal lipoprotein pattern and even for favorably affecting coronary outcomes (Brown et al., 1990). The disadvantages of the combination lie mainly in the side effect profile of nicotinic acid. There is little evidence that the combination is synergistic in producing side effects. Whether the statin-nicotinic acid combination increases the risk for myopathy is uncertain. Some investigators have found that combining relatively small doses of nicotinic acid with a statin produces an improvement in the lipoprotein profile comparable to that obtained with a statin-fibrate combination, and probably with a lower risk for myopathy (Davignon et al., 1994). This potential advantage however may be offset by the inability of some persons to tolerate the side effects of nicotinic acid.

4) Fibrate—nicotinic acid combination therapy

This combination has not been studied extensively, but it is attractive for atherogenic dyslipidemia. In the Stockholm Ischaemic Heart Disease study, a fibrate (clofibrate) + nicotinic acid significantly reduced CHD events in persons with established CHD (Carlson and Rosenhamer, 1988). Otherwise, it is largely untried.

4. Initiation, monitoring and followup of drug treatment

a. Initiation of LDL-lowering drug therapy

Consideration should be given to starting statin therapy for LDL reduction simultaneously with TLC in persons with CHD or a CHD equivalent who have LDL $\geq$130 mg/dL (see previous discussion on drug options when LDL-cholesterol levels are in the range of 100–129 mg/dL). Initiation of drug therapy seems especially advisable when the patient is hospitalized for an acute coronary event or intervention. When therapy is begun in this setting, persons have demonstrated a very high adherence rate, presumably because of the associated importance of the treatment in

preventing recurring events. Early initiation of statin therapy also takes advantage of effects of LDL lowering on endothelial function and plaque stabilization.

Consideration may also be given to starting statin therapy simultaneously with TLC in primary prevention persons who have marked hypercholesterolemia, where it is clear that diet alone will not reduce the patient's LDL cholesterol to goal.

In all other persons, a period of lifestyle modification should precede initiation of drug therapy. This period should be long enough for persons to integrate TLC into their routine and for the effects of this intervention to be manifest. Generally, no more than 3 months is required.

b. Baseline measurements

Prior to initiating drug therapy, baseline lipid and lipoprotein measurements that will be used to follow the drug's efficacy and safety should be documented. Except for acute hospitalization, the initial lipoprotein profile upon which treatment decisions are based should be the average of two measurements done one to four weeks apart while the patient is consistently following a low-fat diet. Baseline measurements also include liver function tests (i.e., ALT or AST), CK and appropriate medical history. Table VI.4–1 lists selected baseline and followup measures for other lipid-modifying drug therapy.

Table VI.4–1. Monitoring Parameters and Followup Schedule

Drug	Monitoring Parameters	Followup Schedule
Bile Acid Sequestrants	Indigestion, bloating, constipation, abdominal pain, flatulence, nausea	Evaluate symptoms initially, and at each followup visit. Also check time of administration with other drugs.
Nicotinic acid	Flushing, itching, tingling, headache, nausea, gas, heartburn, fatigue, rash	Evaluate symptoms initially, and at each followup visit.
	Peptic ulcer	Evaluate symptoms initially, then as needed.
	Fasting blood sugar (FBS) Uric acid	Obtain an FBS and uric acid initially, 6–8 weeks after starting therapy, then annually or more frequently if indicated to monitor for hyperglycemia and hyperuricemia.
	ALT and AST	Obtain an ALT/AST initially, 6–8 weeks after reaching a daily dose of 1,500 mg, 6–8 weeks after reaching the maximum daily dose, then annually or more frequently if indicated.
Statins	Muscle soreness, tenderness or pain	Evaluate muscle symptoms and CK initially. Evaluate muscle symptoms at each followup visit. Obtain a CK when persons have muscle soreness, tenderness, or pain.
	ALT, AST	Evaluate ALT/AST initially, approximately 12 weeks after starting, then annually or more frequently if indicated.
Fibrates	Abdominal pain, dyspepsia, headache, drowsiness	Evaluate symptoms initially, and at each followup visit.
	Cholelithiasis	Evaluate history and symptoms initially, and then as needed.

c. Interval of follow up

With good adherence, maximum LDL lowering, as well as lowering of triglyceride and raising of HDL cholesterol, is achieved within 6 weeks of initiating drug therapy. Thus, the first followup visit should occur 6–8 weeks after initiating drug therapy. In the case of nicotinic acid, where doses must be titrated by the patient to a therapeutic level, the first followup visit should occur 6–8 weeks after the patient has reached the initial targeted dose, generally 1,000–1,500 mg daily. If the dose is increased, monitoring should be continued at 6–8 weeks until the final dose is determined.

If the initial dose of the drug must be increased or another drug added in an effort to reach the treatment goal(s), the patient should be seen in another 6–8 weeks for followup evaluation of the new drug regimen. This process should be repeated until the patient has reached his/her treatment goal(s).

Once the patient has achieved the treatment goal(s), followup intervals may be reduced to every 4–6 months. The primary focus of these visits is encouragement of long-term adherence with

therapy. Lipoprotein profiles should be assessed at least annually, and preferably at each clinic visit to promote compliance.

d. Followup treatment decisions

Followup visits are used to enhance adherence and to determine whether persons have achieved their treatment goal(s). If they have not, changes in the drug regimen should be made to attempt to reach these goals. In most cases, LDL goals can be achieved by titrating doses of the statin or bile acid sequestrant upward to the maximum recommended dose. This may be done systematically one step at a time. For example, the dose of a statin may be doubled at each visit to achieve an additional 6–7 percent LDL lowering with each dose titration. However, when the difference between the patient's on-treatment LDL cholesterol and his/her goal is great, consideration may be given to making larger changes in the drug dose. Alternatively, another LDL-lowering drug may be added (e.g., adding a bile acid sequestrant to a statin), as described above. If the decision is made to replace a less efficacious statin with a more efficacious one to achieve the LDL goal, one statin may be discontinued and the new statin started the next day. A dose titration scheme for commonly used lipid-modifying drugs is presented in Table VI.4–2.

If a patient has high triglycerides ($\geq$200 mg/dL) the non-HDL-cholesterol goal should be addressed. If the patient was earlier treated with a statin to achieve the LDL goal, increasing its dose beyond that used to reach the LDL goal may assist in reaching the non-HDL-cholesterol goal. In many instances, however, reaching the non-HDL-cholesterol goal will require the addition of a triglyceride-lowering drug such as nicotinic acid or a fibrate to the LDL-lowering drug. Clinical experience suggests that if nicotinic acid is selected, the immediate release and polygel sustained-release dosage form (Niaspan®) should be titrated to 1,000–1,500 mg daily by the patient before a followup assessment visit is scheduled. If needed, immediate release nicotinic acid may be further titrated to 3,000 mg daily. If a fibrate is selected, dose titrations are not needed as the initial dose is also the maximum dose. Followup visits for these assessments may also be scheduled 6–8 weeks apart.